REMARKS

Claims 2-10 and 12-20 were pending in this application. Claims 2, 12, and 17-20 have been amended and new claims 29-36 have been added. Claims 3-5, 9, 10, 13-15, 19, and 20 have been withdrawn by the Examiner. Accordingly, upon entry of this amendment, claims 2-10, 12-20, and 29-36 will be pending.

Support for the claim amendments and the new claims presented herein may be found throughout the specification and claims, as originally filed. Specifically, support for the amendments to claims 2 and 12 may be found at, for example, page 12, lines 28-30 of the specification; support for new claims 29-32 may be found in, for example, Examples 2-4, 6, and 9 of the specification; support for new claims 33-36 may be found in, for example, Examples 5, 8, and 11, and page 12, lines 7-33 of the specification.

No new matter has been added. Any amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was performed solely in the interest of expediting prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Objection to Claim 12

The Examiner has objected to claim 12 for a grammatical error.

Applicants respectfully submit that the amendment to claim 12 presented herein renders the Examiner's objection moot. Accordingly, reconsideration and withdrawal of the foregoing objection to claim 12 is respectfully requested.

Rejection of Claims 2, 6-8, 12, and 16-18 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 2, 6-8, 12, and 16-18 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

With respect to claims 2 and 12, and claims 6-8 and 16-18 which depend therefrom, the Examiner is of the opinion that the claims are "indefinite in the recitation of contacting with an agent that 'modulates' expression or activity of PSG-1". Specifically, the Examiner alleges that "[i]t is not clear what direction, degree, or type of 'modulation' is encompassed by the claims". "In addition, said 'modulation' could be intermittent, or constant. Thus, the metes and bounds of the claims cannot be established".

Applicants respectfully traverse this rejection and submit that, based on the plain language of the claim, the teachings in Applicants' specification as well as the knowledge generally available in the art at the time the application was filed, a skilled artisan would find the term "modulate" to be clear and definite. The essential inquiry pertaining to the requirement under 35 U.S.C. §112, second paragraph, is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the application disclosure, the teachings of the prior art and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. M.P.E.P. § 2173.02. In the present case, Applicants' specification is based, at least in part, on the identification of genes which are expressed differentially between effector T cells (Th1 and Th2) and regulatory T cells. Applicants' specification teaches that these differentially expressed genes and gene products may be used to modulate immune responses or to identify agents which would be capable of modulating immune response, by for example, preferentially modulating at least one effector T cell response, without modulating at least one regulatory T cell response, or preferentially modulating at least one regulatory T cell response, without modulating an effector T cell response, each resulting in a shifting or alteration in the balance between tolerance and activation and a modulation in the overall immune response.

Although referencing screening assays, at page 10, lines 13-15, Applicants specification teaches that the molecules of the invention, those preferentially associated with effector T cells or regulatory T cells, may be used to identify compounds which would ***modulate, e.g., upmodulate (mimic or agonize) or downmodulate (antagonize)*** the function of these proteins. Furthermore, at page 13, lines 13-15, Applicants' specification teaches that the agents of the invention are "compounds that ***modulate, e.g., up-modulate or stimulate and down-modulate or inhibit, the expression and/or activity of a molecule of the invention***".

In view of the foregoing, Applicants submit that one of ordinary skill in the art would find the term "modulate" to be clear and definite. The fact that the term "modulate" embraces both up and down modulation and intermittent and constant modulation, does not make the term indefinite. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the foregoing rejection of claims 2, 6-8, 12, and 16-18.

With respect to claim 17, the Examiner is of the opinion that claim17 lacks insufficient antecedent basis for the limitation "said subject".

Applicants respectfully submit that the amendment to claim 17 presented herein renders the Examiner's rejection moot. Accordingly, Applicants request reconsideration and withdrawal of the foregoing rejection of claim 17 under 35 U.S.C. §112, second paragraph.

With respect to claim 18, the Examiner is of the opinion that claim18 lacks insufficient antecedent basis for the limitation "the condition".

Applicants respectfully submit that the amendment to claim 18 presented herein renders the Examiner's rejection moot. Accordingly, Applicants request reconsideration and withdrawal of the foregoing rejection of claim 18 under 35 U.S.C. §112, second paragraph.

Rejection of Claims 2, 6-8, 12, and 16-18 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 2, 6-8, 12, and 16-18 under 35 U.S.C. § 112, first paragraph, "as failing to comply with the written description requirement." In particular, the Examiner is of the opinion that "[t]here is insufficient written description to demonstrate that applicants was in possession of the claimed genus of 'agents' that upmodulate the expression/activity of PSG-1 polypeptide".

Applicants respectfully traverse this rejection for the following reasons. An objective standard for determining compliance with the written description requirement under 35 U.S.C. § 112, first paragraph, is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicant was in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117

(Fed. Cir. 1991) and *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Applicants submit that the instant specification contains sufficient teachings regarding the genus of agents that modulate the expression or activity of a molecule selected from the group consisting of: PSG-1, PSG-3, PSG-6, and PSG-9. For example, at page 13, lines 13-15 the specification teaches that an agent includes compounds that "modulate, *e.g.*, up-modulate or stimulate and down-modulate or inhibit, the expression and/or activity of a molecule of the invention". The specification further teaches exemplary inhibitory compounds, such as, antibodies, RNAi, compounds that mediate RNAi (*e.g.*, siRNA), antisense RNA, dominant/negative mutants of molecules of the invention, peptides, and/or peptidomimetics, and exemplary stimulatory compounds, such as, agonists, which increase the expression and/or activity of molecules of the invention, active protein and nucleic acid molecules, peptides and peptidomimetics of molecules of the invention. See, *e.g.*, page 13, lines 13-26 of the specification. Applicants' specification also teaches the structure, *i.e.*, the nucleotide and amino acid sequence, of PSG-1, PSG-3, PSG-6, and PSG-9 (see, *e.g.*, page 15, lines 26-31 of the specification) and methods routine to one of skill in the art to make and use the nucleotide and amino acid sequences provided as stimulatory and inhibitory agents (see, *e.g.*, page 19, line 23, through page 32, line 26 of the specification).

Furthermore, Applicants specification teaches screening methods to select agents that modulate the expression or activity of a claimed molecule (see, *e.g.*, page 32, line 28, through page 45, line 7 of the specification), exemplary test compounds for use in such methods, for example, small molecules such as peptides, peptidomimetics, nucleic acids, carbohydrates, small organic molecules, and natural product extract libraries, small, organic non-peptidic compounds (see, *e.g.*, page 18, lines 24-31 of the specification), as well as methods of obtaining such compounds (see, *e.g.*, page 46, line 1, through page 47, line 20 of the specification.

Moreover, Applicants submit that it is a well established principle of patent law that "[a] patent need not teach, and preferably omits, what is well known in the art." See M.P.E.P. §2164.01. Applicants submit that agents that modulate the expression and/or activity of PSGs were well known in the art at the time of filing of the application. As evidenced by Appendix A (Aquino, *et al.* (2003) *Pharmacol Res* 49:383), submitted herewith, numerous molecules that stimulate or inhibit the activity of PSGs (members of the CEA family) (see, *e.g.*, Table 1 at page 385 of Appendix A) were well known to one of skill in the art at the time of the invention.

Thus, based on the extensive teachings in Applicants' specification, as well as the knowledge generally available in the art, the skilled artisan would understand that Applicants were in possession of the claimed invention at the time of filing. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 2, 6-8, 12, and 16-18 Under 35 U.S.C. §102

The Examiner has rejected claims 2, 6-8, 12, and 16-18 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent 6,150,326, hereinafter referred to as "the '326 patent". Specifically, the Examiner is of the opinion that "[t]he '326 patent teaches a method for treating autoimmune disease comprising administering a trophoblastic β-1-glycoprotein (TBG)". The Examiner is further of the opinion that the '326 patent

> teaches that the treatment results in correction of the T-suppressor deficit which is present in autoimmune disease by correcting the suppressive activity of T-suppressors. Correction of a T suppressor deficit resulting in increased T suppressor activity would inherently result in the inhibition of effector function relative to regulatory (*i.e.,* suppressor) T cell function.

Applicants respectfully traverse the foregoing rejection under 35 U.S.C. §102 and request reconsideration. For a prior art reference to anticipate a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir.1987). Furthermore, for a prior art reference to inherently anticipate a claimed invention, the extrinsic evidence

> must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. ***The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.***" (See, M.P.E.P. § 2112).

Claim 2, and claims dependent therefrom, are directed to methods for treating a subject having a condition that would benefit from ***modulating the balance of effector T cell function relative to CD4+CD25+ regulatory T cell function in the subject***, comprising administering an agent that modulates the expression or activity of a molecule selected from the group consisting of: PSG-1, PSG-3, PSG-6, and PSG-9 to the subject such that treatment occurs. Claim 12, and claims dependent therefrom, are directed to methods for ***modulating effector T cell function relative to CD4+CD25+ regulatory T cell function in a population of immune cells*** comprising effector T cells and regulatory T cells, comprising contacting the population of cells with an agent that modulates the expression or activity of a molecule selected from the group consisting of: PSG-1, PSG-3, PSG-6, and PSG-9 in at least a fraction of the immune cells such that ***effector T cell function is modulated relative to regulatory T cell function***.

Applicants submit that the'326 patent fails to expressly or inherently anticipate the claimed invention in that the '326 patent fails to teach or suggest that correction in the number of T suppressor cells using the methods disclosed therein ***modulate the balance of effector T cell function relative to CD4+CD25+ regulatory T cell function in the subject***, as required by the pending claims. In fact, nowhere does the '326 patent provide any teachings with respect to effector T cell function or that modulation of at least one effector T cell function alters CD4+CD25+ regulatory T cell activity. Furthermore, the '326 patent fails to teach or suggest monitoring ***the expression of FOXP3, Tbox21 and GATA 3 or the production of TGFβ and Th1 and Th2 cytokines (new claims 32 and 33) after contacting the population of cells with the agent..***

Moreover, with respect to the Examiner's assertions that "[c]orrection of a T suppressor deficit resulting in increased T suppressor activity would inherently result in the inhibition of effector function relative to regulatory (*i.e.,* suppressor) T cell function", Applicants respectfully submit that correction in the ***number*** of T suppressor cells as taught by the '329 patent is not the same as and does not necessarily result in modulation of at least one effector T cell function such that CD4+CD25+ regulatory T cell activity is altered. Rather, the '326 patent teaches a method for treating an autoimmune disease which comprises

> a prestudy of immune status, and in case a deficit of suppressors is determined, then trophoblastic β-I-glycoprotein (TBG) is used as an immune correcting preparation. (see, *e.g.,* column 1, lines 60-64 of the '326 patent).

The '326 patent teaches that the prestudy of immune status comprises determining the responsiveness of cells from a subject to TBG by measuring the suppression index (see, *e.g.*, column 1, line 65, through column 2, line 9 and column 2, line 63, through column 3, line 22 of the '326 patent). In addition, the '326 patent teaches that in case a deficit of suppressors is determined then TBG can be used to correct this deficit in suppressor cells (see, *e.g.*, Column 1, lines 61-63 of the '326 patent). In other words, the '326 patent only teaches methods for increasing the number of T suppressor cells and not for decreasing the activity of effector cells for this specific group of subjects.

However, it is possible that a subject might have a normal number of T suppressor cells but an exuberance of T cell effector activity which would present as a T suppressor cell deficit. In such a case, the methods of the '326 patent ***would not necessarily result in*** ***the inhibition of effector T cell function relative to CD4+CD25+ regulatory T cell function***, since the methods do not inhibit effector T cell function and there is no deficit in T suppressor cell number.

In further support of this position, Applicants also submit herewith Appendices B-D (von Herrath, *et al.* (2002) *J Immunol.* 168:933-41; Chatenoud *et al.* (1994) *Proc Natl Acad Sci U S A*. 91:123-7; and Bushell *et al.* (2005) *J Immunol.* 174:3290-7) ***each of which demonstrate that modulation of regulatory T cell function does not necessarily result in modulation of effector T cell function***. For example, von Herrath, *et al.* teach that administration of a nonmitogenic CD3 antibody restores self-tolerance in a mouse model of nonobese autoimmune diabetes and that "competence to clear viral infections was maintained. Thus, administration of nonmitogenic CD3 prevents diabetes by sufficient systemic reduction of (auto)aggressive lymphocytes, but without compromising antiviral immune competence" (see, *e.g.*, the Abstract of von Herrath *et al.*). Similarly, Chatenoud *et al.* teach that mice treated with anti-CD3 antibodies to treat autoimmune diabetes rejected histoincompatible skin grafts normally, whereas they did not destroy syngeneic islet grafts, unlike control untreated overtly diabetic NOD females" (see, *e.g.*, the Abstract of von Chatenoud *et al.*). Finally, Bushell *et al.* teach that in animals treated with anti-CD4 antibody treatment to prevent allograft rejection "[n]either virus-specific CTL activity *in vitro* nor the clearance of virus *in vivo* was significantly diminished" (see, *e.g.*, the Abstract of von Bushell *et al.*).

Based on all of the foregoing, it is evident, based on the foregoing, that ***modulating the balance of effector T cell function relative to CD4+CD25+ regulatory T cell function*** is not the same as increasing suppressor cell number in individuals determined to have a deficit in suppressor cell number disclosed by the '326 patent and, thus, the'326 patent fails to inherently or expressly anticipate the claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Dated: December 4, 2007

Respectfully submitted,

By______________________
Deborah L. Nagle
Registration No.: 59,978
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney For Applicants